REMARKS

The Office Action of February 10, 2005 has been received and reviewed. Claims 1-6, 8-12, 14-24, 29-34, and 38 are currently pending, and all pending claims stand rejected. All amendments and claim cancellations are made without prejudice or disclaimer. Reconsideration is respectfully requested.

Applicants would like to thank the Office and Examiners for the time and courtesy extended in the interview of June 9, 2005. During the interview it was agreed to direct the claims to a specific tumor cell (Kaposi's Sarcoma), and have the combination of gene markers be SEQ ID NOS: 72 and 81. Specifically, claims 1, 21, and 33 are to be directed to Kaposi's Sarcoma and SEQ ID NOS: 72 and 81. Furthermore in response to the Office Action, applicants are to elucidate data with regard to SEQ ID NOS: 72 and 81. Applicants respectfully note that during the interview the Examiner agreed to examine the application with regard to SEQ ID NOS: 72 and 81. Applicants acknowledge and agree with the content of the interview summary. Applicants respectfully invite the Office to contact the undersigned agent with any further questions regarding the interview.

Applicants wish to note that amended claim 19 is directed in part to the expression products of Tie 1 and SialoAdhesin. As explained in Example 9, TAG015 and TAG032 represent sub-sequences of Tie 1 and SialoAdhesin respectively. Furthermore, SEQ ID NOS: 72 and 81 are sub-sequences of Tie 1 and SialoAdhesin with the addition of a poly-A tail. As such, applicants respectfully submit that claims to the expression products of Tie 1 and SialoAdhesin are enabled as SEQ ID NOS: 72 and 81 are enabled and generally represent sub-sequences of Tie 1 and SialoAdhesin.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 12, 19, 33, and 38 stand rejected under 35 U.S.C. §112, second paragraph, as assertedly being vague and indefinite. At least partially in view of the amendments to the claims, applicants respectfully submit that claims 1, 12, 19, 33, and 38 are definite.

Specifically, it was thought that it was unclear as to whether claim 1 was intended to be limited to determining whether a sample comprises an expression product of a marker gene or for

determining whether a treatment is effective in changing a status of a certain set of target cells in an individual as referred to in the preamble. (*See*, Office Action mailed February 10, 2004, page 3). Although the applicants do not agree that any of the claims are indefinite, to expedite prosecution, claim 1 has been amended. As amended, claim 1 is directed to determining whether a treatment is effective in changing a status of Kaposi's Sarcoma tumor cells in an individual.

With regard to claim 12, it was thought that it was unclear as to whether claim 12 was intended to be limited to determining whether a nucleic acid hybridized in a sample or for detecting an expression product of a marker gene. (*See*, Office Action mailed February 10, 2004, page 3). Although the applicants do not agree that any of the claims are indefinite, to expedite prosecution, claim 12 has been amended. As amended, claim 12 is directed to detecting hybridized expression products of SEQ ID NOS: 72 and 81.

With regard to claim 19, it was thought that it was unclear as to whether claim 19 was intended to be limited to determining whether a sample comprises an expression product of at least one marker gene or for determining whether an individual possesses a tumor cell and/or site of angiogenesis. (*See*, Office Action mailed February 10, 2004, pages 3-4). Although the applicants do not agree that any of the claims are indefinite, to expedite prosecution, claim 19 has been amended. As amended, claim 19 is directed to determining whether an individual possesses a Kaposi's Sarcoma tumor cell and/or a site of angiogenesis.

With regard to claim 33, it was thought that it was unclear as to whether claim 33 was intended to be limited to detecting the level of PBMC expression of at least one of the SEQ ID NOS or for determining the presence of a tumor cell in an individual. (*See*, Office Action mailed February 10, 2004, page 4). Although the applicants do not agree that any of the claims are indefinite, to expedite prosecution, claim 33 has been amended. As amended, claim 33 is directed to determining the presence or absence of a Kaposi's Sarcoma tumor cell in an individual.

With regard to claim 38, it was thought that it was unclear as to whether claim 38 was intended to be limited to quantifying an expression product of at least one marker gene in a sample or for determining whether an individual posses a tumor cell and/or site of angiogenesis. (*See*, Office Action mailed February 10, 2004, pages 4-5). Although the applicants do not agree

that any of the claims are indefinite, to expedite prosecution, claim 38 has been amended. As amended, claim 38 is directed to determining whether an individual possesses a Kaposi's Sarcoma tumor cell and/or a site of angiogenesis.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-6, 8-12, 14-24, 29-34, and 38 stand rejected under 35 U.S.C. §112, first paragraph, as assertedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejections as hereinafter set forth.

Applicants respectfully note that the rejections of claims 2, 6, 8, 20, and 22-23 are moot as those claims have been cancelled herein.

A) No teaching of the most appropriate detection system

As indicated in the Office Action, it was thought that specification does not teach the most appropriate expression detection system to detect expression of a marker gene. (*See*, Office Action mailed February 10, 2004, pages 6-7). Applicants respectfully note that the amended claims are directed to the detection of expression of SEQ ID NOS: 72 and 81. In addition, as noted by the Examiner, the level of skill in the art is high. (*See*, Office Action mailed February 10, 2004, page 12). Furthermore, the specification, at ¶10, indicates that a person of skill in the art is well capable of designing the most appropriate expression detection system to practice this embodiment. As would be apparent to one of high skill, certain expression detection systems may be more appropriate than others based on the characteristics of the expression product to be detected, expression levels, cost, and availability of reagents. The systems one of skill in the art could select from are well known in the art and include, but are not limited to, northern blots, nuclease protection assays, cDNA production, DNA micro array analysis, PCR, SAGE, ribozymes, gel electrophoresis of DNA, RNA, cDNA, or proteins, or fragments thereof, immunoprecipitation, immunohistochemistry, in-situ hybridization, and immunoblotting. Design of such detection systems is routine in the practice of molecular biology and well within the high level of skill in the art. As such, applicants respectfully submit that one of skill in the art could

select and design the most appropriate system for detecting expression products of SEQ ID NOS: 72 and 81.

B) No teaching as to change in expression levels indicating growth of blood vessels

As noted in the Office Action, it was thought that the specification does not teach how much change in expression level of the detection marker indicates active growth of blood vessels. (*See*, Office Action mailed February 10, 2004, pages 7-8). However, the specification at ¶10, indicates that any change in a marker gene may indicate the active growth of blood vessels. Specifically: "[i]n the extreme cases, the level of expression product can range from detectable to not detectable. Marker genes displaying such zero-to-one relation in expression product levels are preferred in the present invention. A zero-to-one relation can be used to design relatively simple test systems." In a zero-to one relationship, any change is indicative and thus applicants respectfully submit that the specification does teach how much of a change in the expression level of a detection marker may indicate active growth of blood vessels.

Furthermore, ¶23 of the specification provides that "a nucleic acid comprising a sequence as depicted in FIGS. 1-18 (SEQ ID NOS:65-82) and/or Table 1 (SEQ ID NOS:1-20) or Table 2 (SEQ ID NOS:21-31) can be used as a detection marker for the process of angiogenesis in the course of regenerative treatment." In relation to these detection markers for angiogenesis (the active growth of blood vessels), Table 1 provides an "overexpression factor." Therein, overexpression factors as little as two fold and as great as 30 fold are given as examples of changes indicating the active growth of blood vessels. As such, applicants respectfully submit, as supported by the specification, any change in the expression level of the detection marker may indicate the active growth of blood vessels. Furthermore, applicants respectfully submit that Table 1 provides specific examples of changes in expression level that can be used as a marker for the process of angiogenesis.

In addition, applicants respectfully note that the amended claims are directed to SialoAdhesin and TIE 1 and parts or analogues of these two genes. As indicated in the specification at ¶12, Kaposi's Sarcoma is a disease of proliferating blood vessels. As shown in Figure 19, SEQ ID NO 72 (as measured through TAG015) is increased in Kaposi's Sarcoma and

therefore increased levels of SEQ ID NO 72 expression products indicate a growth of blood vessels. Turning now to Figure 20, SEQ ID NO 81 expression (as measured through TAG032) is increased the PBMCs of Kaposi's Sarcoma patients and therefore increased levels of SEQ ID NO 81 expression products indicate a growth of blood vessels. These results were later confirmed by Cornelissen et al. following the teachings of the specification. (Cornelissen et al., "Gene expression profile of AIDS-related Kaposi's sarcoma", BMC cancer, 2002, 2, 21). Therein, the investigators used the same SAGE system taught in the specification to show seven fold increases in the expression products of SEQ ID NOS: 72 and 81 (Tie 1 and SialoAdhesin respectively) associated with the growth of blood vessels in Kaposi's Sarcoma (*Id.* at Table 5). As such, applicants respectfully submit that, as shown in the specification and confirmed by later work following the guidance of the specification, increased levels of SEQ ID NOS: 72 and 81 indicate the growth of blood vessels.

C) No guidance as to how absence of a marker is indicative of a disease

In addition, it was thought that the specification does not give any guidance on how to determine if the absence of the marker gene is indicative of a disease, developing a disease, or not have having a disease at all, or how to determine if an expression amount is beneficial or harmful. (*See*, Office Action mailed February 10, 2004, page 8).

Applicants respectfully submit that the claims, as amended, are not directed to the absence of a marker gene being indicative of a disease, developing a disease, or not have having a disease at all. Furthermore, applicants respectfully submit that the claims, as amended, are not directed to determining if an expression amount is beneficial or harmful. As such, applicants respectfully submit that the above noted rejection under 35 U.S.C. § 112, first paragraph does not apply to the claims as amended and is therefore moot.

D) No guidance as to determining the presence of a non-hemopoetic cell.

Additionally, it was thought that the specification provides no guidance how to determine if the altered amount of expression is indicative of the presence of a non-hemopoietic cell. (*See*, Office Action mailed February 10, 2004, page 8). Applicants respectfully submit that the

application does not claim the use of an altered amount of expression to determine the presence of a non-hemopoetic cell. As such, applicants respectfully submit they are not required to enable such a determination. In addition, it would be well within the abilities of one of skill in the art to analyze a sample to determine if it contained non-hemopoetic cells. Markers for hemopoetic cells are well known in the art (*See, e.g.* the makers used in: Sirianni et al., "Gamma-Interferon Production in the Peripheral Blood Mononuclear Cells and Tumor Infiltrating Lymphocytes from Kaposi's Sarcoma Patients: Correlation With the Presence of Human Herpesvirus-8 in Peripheral Blood Mononuclear Cells and Lesional Macrophages", Blood, 91, 3, 1998; Jones, Hemopoetic System, Springer Verlag 1990) and are routinely used to determine the presence of hemopoetic cells.

E) Results thought to be not statistically significant

The Office Action indicates that it was thought that the specification provided no indication as to whether the results were statistically significant such that the skilled artisan would be able to predictably correlate the results with the presence of a tumor cell, diagnosis of a disease, or efficacy of a treatment. (*See*, Office Action mailed February 10, 2004, page 9). Applicants respectfully note that the amended claims are directed to SEQ ID NOS: 72 and 81. Applicants respectfully submit that they are not required to guarantee 100% success of the methods in the course of enabling others to practice the invention. Enablement only requires that any person skilled in the art is able to make or use the invention. Moreover, in Figures 19 and 20, the data for TAG015 (Fig. 19, indicating SEQ ID NO: 72 (Tie 1)) and TAG032 (Fig. 20, indicating SEQ ID NO: 81 (SialoAdhesin)) have error bars which do not overlap, suggesting that these results are statistically significant and can be predictably correlated with the results. In addition, persons using the methods outlined in the specification were enabled to gain consistent results. (See, Cornelissen et al., "Gene expression profile of AIDS-related Kaposi's sarcoma", BMC cancer, 2002, 2, 21). Specifically, the data presented in Figure 3 therein for Tie 1 indicate a statistically significant level of change ($P<0.05$). As such, given the that the applicants are not required to guarantee a result, that the specification provides statistically significant changes, and that the specification enabled the practice of the invention showing a statistically significant

change, the applicants respectfully submit that the specification is enabling such that a skilled artisan would be able to predictably correlate a change in the levels of SEQ ID NOS: 72 and 81 with the presence of a tumor cell.

F) No teaching as change of expression of SEQ ID NO: 81 indicating presence of a target cell or indicating if a treatment is effective.

Lastly, it was thought that the specification does not teach how to determine how much of a change in expression in SEQ ID NO 81 would indicate the presence of a target cell of any disease. It was additionally thought that the specification lacks guidance on how the specific marker genes found in the study on KS are suitable for determining if any treatment is effective.

As can be noted by a comparison of SEQ ID NO: 30 (*see* ¶ 54) and SEQ ID NO: 81 (*see* ¶ 97), SEQ ID NO: 81 includes, in its entirety, SEQ ID NO: 30. As described in Example 9, the overlap in the sequence between SEQ ID NOS: 30 and 81 allows SEQ ID NO: 30 to be used as a surrogate or tag for monitoring the expression of SialoAdhesin (part of which is presented as SEQ ID NO: 81). As can be seen in Table 2, SEQ ID: 30, and thus the expression level of SEQ ID NO: 81 is increased 2-10 fold in Kaposi's Sarcoma. Thus, applicants respectfully submit that specification does teach how much of a change in expression in SEQ ID NO 81 indicates indicate the presence of a target cell in Kaposi's Sarcoma. In addition, persons using the guidance of the specification have shown that specific marker genes found in the study on KS are suitable for determining if any treatment is effective. (*See*, van der Kuyl et al., "Primary effect of chemotherapy on the transcription profile of AIDS-related Kaposi's sarcoma" BMC cancer, 2002, 2, 21) In van der Kuyl et al. it was , for example, shown that the levels of TIMP fall to normal levels upon treatment (Table 5). Thus, as provided in ¶10, a change in the level of the expression product (TIMP in this case) is indicative for whether a treatment was effective. As such, applicants respectfully submit, that a person of skill in the art, following the guidance of the specification is enabled to determine if a treatment is effective using a marker gene.

Rejections under 35 U.S.C. § 102

Sager

Claims 1-3, 9-10, 19, and 29 are rejected under 35 U.S.C. 102(b) as assertedly being anticipated by Sager. Applicants respectfully traverse the rejections as set forth herein.

Sager cannot anticipate claim 1 as it does not expressly or inherently describe each and every element of claim 1. (*See, Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir 1987)). Amended claim 1 directs that a determination be made of whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Sager does not expressly or inherently disclose determining whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Thus, amended claim 1 cannot be anticipated by Sager.

Furthermore, applicants respectfully submit that claims 2-3, 9-10, and 29 are novel, at the very least, as depending from novel independent claim 1.

Sager cannot anticipate claim 19 as it does not expressly or inherently describe each and every element of claim 19. (*Id.*). Amended claim 19 directs the determination of whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Sager does not expressly or inherently disclose determining whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Thus, amended claim 19 cannot be anticipated by Sager.

Miles

Claims 1-3, 9-11, and 19 are rejected under 35 U.S.C. 102(b) as assertedly being anticipated by Miles. Applicants respectfully traverse the rejections as set forth herein.

Miles cannot anticipate claim 1 as it does not expressly or inherently describe each and every element of claim 1. (*Verdegaal Brothers,* 2 USPQ2d at 1053). Amended claim 1 directs that a sample be obtained after initiating the treatment. Miles does not expressly or inherently disclose obtaining the sample after beginning treatment. All treatments of samples described by Miles occur after the sample has been obtained.

Furthermore, amended claim 1 directs that a determination be made of whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Miles does not expressly or inherently disclose determining whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. As such, applicants respectfully assert that, for at least the foregoing reasons, amended claim 1 cannot be anticipated by Miles.

Furthermore, applicants respectfully submit that claims 2-3, and 9-11 are novel, at the very least, as depending from novel independent claim 1.

Miles cannot anticipate claim 19 as it does not expressly or inherently describe each and every element of claim 19. (*Id.*). Amended claim 19 directs the determination of whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Miles does not expressly or inherently disclose determining whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Thus, amended claim 19 cannot be anticipated by Miles.

Brown

Claims 1-3, 6, 9-11, 19, and 21-22 are rejected under 35 U.S.C. 102(b) as assertedly being anticipated by Brown. Applicants respectfully traverse the rejections as set forth herein.

Brown cannot anticipate claim 1 as it does not expressly or inherently describe each and every element of claim 1. (*Verdegaal Brothers,* 2 USPQ2d at 1053). Amended claim 1 directs that a sample be obtained after initiating the treatment. Brown does not expressly or inherently disclose treating an individual or obtaining a sample from an individual after beginning treatment. Brown discloses no treatments, only the mRNA expression levels in samples from individuals.

Furthermore, amended claim 1 directs that a determination be made of whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Brown does not expressly or inherently disclose determining whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. As such, applicants respectfully assert that, for the foregoing reasons, amended claim 1 cannot be anticipated by Brown.

Furthermore, applicants respectfully submit that claims 2-3, 6, and 9-11 are novel, at the very least, as depending from novel independent claim 1.

Brown cannot anticipate claim 19 as it does not expressly or inherently describe each and every element of claim 19. (*Id.*). Amended claim 19 directs the determination of whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Brown does not expressly or inherently disclose determining whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Thus, amended claim 19 cannot be anticipated by Brown.

Brown cannot anticipate claim 21 as it does not expressly or inherently describe each and every element of claim 21. (*Id.*). Amended claim 21 directs the determination of whether a hemopoietic cell from said individual comprises an altered amount of expression products of SEQ ID NOS: 72 and 81 as compared with reference values. Brown does not expressly or inherently disclose determining whether a hemopoietic cell from said individual comprises an altered amount of expression products of SEQ ID NOS: 72 and 81 as compared with reference values. Thus, amended claim 21 cannot be anticipated by Sirianni.

Claim 22 is novel, at the very least, as depending from novel independent claim 21.

Sirianni

Claims 1-3, 6, 9-11, 19, 21-22, 24, and 29-30 are rejected under 35 U.S.C. 102(b) as assertedly being anticipated by Sirianni. Applicants respectfully traverse the rejections as set forth herein.

Sirianni cannot anticipate claim 1 as it does not expressly or inherently describe each and every element of claim 1. (*Verdegaal Brothers,* 2 USPQ2d at 1053). Amended claim 1 directs tha sample be obtained after initiating the treatment. Sirianni does not expressly or inherently disclose treating an individual or obtaining a sample from an individual after beginning treatment. Sirianni discloses no treatments, only the expression levels in samples from untreated individuals.

Furthermore, amended claim 1 directs that a determination be made of whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Sirianni does not

expressly or inherently disclose determining whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. As such, Applicants respectfully assert that, for the foregoing reasons, amended claim 1 cannot be anticipated by Sirianni.

Furthermore, applicants respectfully submit that claims 2-3, 6, 9-11, and 29-30 are novel, at the very least, as depending from novel independent claim 1.

Sirianni cannot anticipate claim 19 as it does not expressly or inherently describe each and every element of claim 19. (*Verdegaal Brothers,* 2 USPQ2d at 1053). Amended claim 19 directs the determination of whether the sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Sirianni does not expressly or inherently disclose determining whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Thus, amended claim 19 cannot be anticipated by Sirianni.

Sirianni cannot anticipate claim 21 as it does not expressly or inherently describe each and every element of claim 21. (*Id.*). Amended claim 21 directs the determination of whether a hemopoietic cell from said individual comprises an altered amount of expression products of SEQ ID NOS: 72 and 81 as compared with reference values. Sirianni does not expressly or inherently disclose determining whether a hemopoietic cell from said individual comprises an altered amount of expression products of SEQ ID NOS: 72 and 81 as compared with reference values. Thus, amended claim 21 cannot be anticipated by Sirianni.

Furthermore, applicants respectfully submit that claims 22 and 24 are novel, at the very least, as depending from novel independent claim 21.

Sonis

Claims 1, 4-5, 9-10, and 19 are rejected under 35 U.S.C. 102(b) as assertedly being anticipated by Sonis. Applicants respectfully traverse the rejections as set forth herein.

Sonis cannot anticipate claim 1 as it does not expressly or inherently describe each and every element of claim 1. (*Verdegaal Brothers,* 2 USPQ2d at 1053). Amended claim 1 directs that a determination be made of whether there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Sonis does not expressly or inherently disclose determining whether

there is a change in the level of the expression products of SEQ ID NOS: 72 and 81. Thus amended claim 1 cannot be anticipated by Sonis.

Furthermore, applicants respectfully submit that claims 4-5, and 9-10, are novel, at the very least, as depending from novel independent claim 1.

Sonis cannot anticipate claims 19 as it does not expressly or inherently describe each and every element of claim 19. (*Id.*). Amended claim 19 directs the determination of whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Sonis does not expressly or inherently disclose determining whether said sample comprises expression products of SialoAdhesin or a part or analogue thereof and TIE 1 or part or analogue thereof. Thus amended claim 19 cannot be anticipated by Sonis.

Statutory Double Patenting

Claims 1-6, 9-10, 19, 21-22, 24, and 29-30 stand provisionally rejected under 35 U.S.C. §101 as assertedly claiming the same invention as described in U.S. Patent Application 10/310,677. Applicants respectfully submit that the claims of the present application, as amended, are no longer coextensive in scope with the claims of U.S. Patent Application 10/310,677. For example, claim 1 of the present application in part directs that a determination be made of whether there is a change in the level of the expression products SEQ ID NOS: 72 and 81. Claim 1 of U.S. Patent Application 10/310,677 directs a determination of whether a sample comprises an expression product of a marker gene.

As independent claims 1, 12, 19, 21, 32-34, and 38, as amended herein, are not coextensive with the claims of U.S. Patent Application 10/310,677, applicants respectfully request that the Statutory Double Patenting rejection of these claims be withdrawn. Furthermore, as all other rejected claims depend directly or indirectly from independent claims 1, 12, 19, 21, 32-34, and 38, applicants respectfully request that the Statutory Double Patenting rejection of these claims be withdrawn as well.

Non-Statutory Double Patenting

Claims 6, 11-12, 14, 18, 20, 23, and 31-33 are provisionally rejected as assertedly violating he judicially created doctrine of obvious type double patenting in view of the claims of U.S. Patent Application 10/310,677. Applicants assert that if the current provisional non-statutory double patenting rejection ever ripens, the claims of the remaining application will be amended to remove the non-statutory double patenting rejection or that a terminal disclaimer will be filed.

CONCLUSION

In light of the above amendments, claim cancellations, and remarks, applicants respectfully request reconsideration of the application. If there are any questions concerning the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Examiner is respectfully invited to contact applicants' undersigned agent.

Respectfully submitted,

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